

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 February 2001 (08.02.2001)

PCT

(10) International Publication Number
WO 01/08673 A1

(51) International Patent Classification⁷: A61K 31/135

NEMETH, Edward, F. [US/US]; 4414 Zarahemla Drive,
Salt Lake City, UT 84124 (US).

(21) International Application Number: PCT/US00/20834

(22) International Filing Date: 31 July 2000 (31.07.2000)

(74) Agents: SIMON, Soma, G. et al.; SmithKline Beecham
Corporation, Corporate Intellectual Property, UW2220,
709 Swedeland Road, P.O. Box 1539, King of Prussia, PA
19406-0939 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/146,778 31 July 1999 (31.07.1999) US

(81) Designated States (*national*): AE, AL, AU, BA, BB, BG,
BR, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK,
MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ,
UA, US, UZ, VN, YU, ZA.

(71) Applicants (*for all designated States except US*):
SMITHKLINE BEECHAM CORPORATION
[US/US]; One Franklin Plaza, Philadelphia, PA 19103
(US). NPS PHARMACEUTICALS, INC. [US/US]; 420
Chipeta Way, Salt Lake City, UT 84108 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): GOWEN, Maxine
[GB/US]; 280 S. Roberts Road, Bryn Mawr, PA 19010
(US). SUVA, Larry, J. [AU/US]; 161 Eaton Drive, Wayne,
PA 19087 (US). FOX, John [GB/US]; 4594 Stockbridge
Lane, Salt Lake City, UT 84117 (US). STROUP, George,
B. [US/US]; 303 Brighton Circle, Devon, PA 19333 (US).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/08673 A1

(54) Title: CALCILYTIC COMPOUNDS

(57) Abstract: Novel methods of treating bone diseases or disorders are provided.

topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

- 5 As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include bone and mineral-related diseases or disorders; hypoparathyroidism; those of the central nervous system such as seizures, stroke,
10 head trauma, spinal cord injury, hypoxia-induced nerve cell damage, such as occurs in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and
15 Tourette's syndrome; diseases involving excess water reabsorption by the kidney, such as syndrome of inappropriate ADH secretion (SIADH), cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (*e.g.*, aminoglycoside antibiotics); gut motility disorders such as diarrhea and spastic colon; GI ulcer diseases; GI diseases with
20 excessive calcium absorption such as sarcoidosis; autoimmune diseases and organ transplant rejection; squamous cell carcinoma; and pancreatitis.

In a preferred embodiment of the present invention, the present compounds are used to increase serum parathyroid ("PTH") levels in a non-pulsatile manner. Increasing serum PTH levels may be helpful in treating diseases such as
25 hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease and osteoporosis.

The normal range for intact PTH in humans is about 10 to about 65 pg/ml. Increasing serum PTH may also be useful to prophylactically retard or prevent the onset of a disease. Prophylactic treatment can be performed, for example, on a
30 person with a low serum PTH, or a person without low serum PTH, but where increasing PTH has a beneficial compensating effect. Preferably, the patient has an

101
02
P. 11/11

*calcilytic compound
is a compound able to
inhibit CaR activity*

What is claimed is:

1. A method of treating a disease or disorder characterized by an abnormal bone or mineral homeostasis which comprises administering to a subject in need of treatment thereof an effective amount of a calcilytic compound in conjunction with an effective amount of an anti-resorptive agent.
2. A method according to claim 1 wherein the calcilytic compound is selected from the group consisting of:
 - N-[(2R-Hydroxy-3-[(3-chloro-2-cyano)phenoxy-propyl]-1,1-dimethyl-2-(2-naphthyl)ethyl amine hydrochloride;
 - N-[(2R-Hydroxy-3-[(3-chloro-2-cyano)phenoxy-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl amine hydrochloride;
 - N-[(2R-Hydroxy-3-[(2,3-dichloro)phenoxy-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl amine hydrochloride;
 - 15 N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(6-(1,2,3,4-tetrahydronaphthyl)ethylamine;
 - N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(Benzothien-3-yl)-ethylamine;
 - N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(Benzothien-2-yl)-ethylamine;
 - 20 N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(decahydronaphthalen-2-yl)ethylamine;
 - N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-4-phenylbutylamine;
 - 25 N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-4-(2-methoxyphenyl)butylamine;
 - N-[2R-Hydroxy-3-[[2-cyano-4-[N-methyl-N-[4-ethylcarboxyphenyl)sulfonyl]-amino]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine;
 - N-[2R-Hydroxy-3-[[2-cyano-4-[N-methyl-N-[3-
 - 30 methylcarboxymethoxyphenyl)sulfonyl]-amino]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine;